REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

II. Summary of Claims and Amendments Thereto

Claims 1-50 are pending in this application. Claims 41-45, 47 and 48 have been withdrawn from consideration by the Examiner in view of the restriction requirement, which has been made final. Claims 1, 8 and 39 have been amended and claims 49-55 are presented anew.

Claim 1 has been amended to clarify that the claimed plasmin inhibitor preparation is substantially pure with respect to the recited percentage concentrations of plasmin inhibitor. Support for this amendment can be found in the specification at page 20, lines 14-24.

Claims 8 and 39 have been amended to delete the recitation of biologically active fragments, variants or derivatives. Claim 39 is also amended so that it depends from amended claim 9.

Claim 9 has been amended to reflect its dependency upon claim 1 and to clarify that the claimed plasmin inhibitor comprises a polypeptide having the general formula defined in that claim.

Newly added claim 49 depends from amended claim 1 and further defines the plasmin inhibitor as comprising the amino acid sequence ECESTCAA, which represents an amino acid sequence conserved between all the exemplified plasmin inhibitor polypeptides (both mature and unprocessed). Support for this amendment can be found in the specification as originally filed at least in Figure 11, and particularly in the clearly demarcated "ECESTCAA" consensus region shown in that figure.

Newly added claim 50 depends from amended claim 1 and further defines the plasmin inhibitor as comprising the amino acid sequence NANNF. Like the amino acid sequence

ECESTCAA recited in claim 49, the sequence NANNF is present in all the exemplified plasmin inhibitor polypeptides (both mature and unprocessed) and is supported in the specification as originally filed at least in Figure 11, and particularly in the corresponding demarcated "NANNF" consensus region shown in that figure.

Newly added claim 51 further defines the plasmin inhibitor defined in claim 49 as further comprising the amino acid sequence YGGC. This represents another sequence conserved between the exemplified plasmin inhibitor polypeptides (both mature and unprocessed) and is supported in the originally filed specification at least in the corresponding demarcated "YGGC" consensus region shown in Figure 11.

Newly added claim 52 depends from amended claim 1 and further recites that the plasmin inhibitor is conjugated to an anti-fibrin antibody. This amendment finds support in the specification as originally filed at least at page 12, lines 26-28, page 42 line 1 to page 43, line 9, in Example 3 and in original claim 48.

Newly added claims 53-55 further define the purity of the composition of claim 1. Support for these claims can be found in the specification at page 20, lines 14-24.

For the foregoing reasons, the amendments and additions made herein are fully supported by the specification and do not include new matter. Entry of the amendments is respectfully solicited.

III. The Office Action

A. Objections to the Claims

Claims 4 and 8 were objected to for various informalities. Office Action at page 2. Applicants respectfully submit that the amendments to the claims render moot these objections.

In particular, the Examiner objected to claim 4, allegedly because the claim is missing the term "sec^{-1}" in the range value. No amendment is required because claim 4 defines the dissociation constant of the claimed plasmin inhibitor for plasmin, and not the dissociation

rate constant as recited, for example, in claims 5-7. The dissociation constant recited in claim 4 is clearly supported in the specification as originally filed at least at page 5, lines 13-14.

B. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 8-40 and 46 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for: (a) fragments of the plasmin inhibitors set forth in SEQ ID NOs: 2, 4, 6, 8, 10 and 12, (b) variants/derivatives other than those defined in claims 9-38, or (c) *in vivo* alleviation of blood loss. To the extent that this rejection may apply to the claims as amended, Applicants respectfully traverse the rejection.

The rejection, in so far as it relates to items (a) and (b), has been rendered moot by the amendments to the claims. Thus, the claims do not recite the offending fragments, variants, and derivatives.

As to item (c), Applicants believe the Examiner is mistaken in alleging a lack of enabling disclosure for the *in vivo* use of the claimed polypeptides to alleviate blood loss. In this context, Applicants kindly draw the Examiner's attention to the experimental data collected under the sub-heading "*Behaviour of Txlns in an animal bleeding model*". *See* specification page 50, line 18, through page 51, line 14. These data explicitly demonstrate the beneficial effect of intravenous delivery of the recited plasmin inhibitors, namely Textilinins 1 and 2, on the blood loss from an excised mouse tail vein.

Consequently, the claimed invention fully complies with the strictures of the enablement requirement. Accordingly, Applicants respectfully urge the Examiner to reconsider and withdraw the rejection.

C. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1-40 and 46 stand rejected under 35 U.S.C. § 112, second paragraph, for being allegedly indefinite because the term "substantially pure" is not properly defined. According to the Examiner, the term encompasses only a typical definition. Applicants respectfully traverse this ground for rejection.

Applicants have amended the claims to define the term by incorporating explicit reference to percentage concentrations of the recited plasmin inhibitor. Additionally, Applicants kindly submit that defining their invention is well within their purview under § 112, second paragraph. Accordingly, Applicants have sought to distinctly claim and particularly point out the term "substantially pure" by reference to an objective and ascertainable standard, *i.e.*, percentage concentrations. Therefore, the amendments should moot the Examiner's concerns. Accordingly, the Examiner is respectfully urged to reconsider and withdraw the rejection.

D. Anticipation Rejections

1. Masci et al.

Claims 1-40 and 46 stand rejected under 35 USC § 102(a) as being allegedly anticipated by WO 99/58569 to Masci et al. ("Masci"), which is the published International application, *i.e.*, PCT/AU99/00343, to which the present application claims convention priority. Specifically, the Examiner asserted that because inventorship in the International application is different from that of present application, the chain of priority is severed, which would render Applicants' published international application available as prior art. Applicants respectfully traverse this rejection.

The PCT Request of the underlying International application PCT/AU99/00343 was legitimately amended under PCT Rule 92*bis* to list the correct inventors and the corrected Request is subsequently treated therefore as the PCT Request of the International application. Accordingly, the Oath or Declaration filed for the present application names the same inventive entity as the inventive entity set forth in the International application.

As noted correctly by the Examiner, "[t]he inventorship of an international application entering the national stage under 35 U.S.C. 371 is that inventorship set forth in the international application, which includes any change effected under PCT Rule 92*bis*." 37 C.F.R. § 1.41(a)(4). With respect to such a change *subsequent* to the execution of any oath or declaration filed under PCT Rule 4.17(iv), the procedures under 37 C.F.R. § 1.497(d) and (f)

apply. *Id.* For the reasons below, Applicants are not obligated by the strictures of 37 C.F.R. § 1.497.

37 C.F.R. § 1.497(d) requires a statement from each person being added as an inventor and from each person being deleted as an inventor that any error in inventorship in the International application occurred without deceptive intention on his or her part. However, the Examiner will note that this statement is *only* required if either one of the following conditions is met:

(i) The oath or declaration filed for the present application names an inventive entity different from the inventive entity set forth in the International application. Importantly, this condition is not triggered merely because the inventive entity here is different from the inventive entity set forth in the International application *as originally filed.* This condition does not pertain here. It is possible to correct errors in the PCT Request under Rule 92*bis*. Accordingly, the Request so corrected is subsequently treated as the PCT Request of the International application.

(ii) A change to the inventive entity has been effected under PCT Rule 92*bis* subsequent to the execution of any oath or declaration which was filed in the application under PCT Rule 4.17(iv) and the inventive entity thus changed is different from the inventive entity identified in any such oath or declaration. Accordingly, changes to the inventive entity effected under PCT Rule 92*bis* are only relevant if an oath or declaration under PCT Rule 4.17(iv) is executed in respect of the related International application. This condition also does not pertain here for the reasons below.

PCT Rule 4.17(iv) specifies that the PCT Request may, for the purposes of the National Law applicable in one or more designated states (*e.g.*, the United States), contain one or more of the following declarations, worded as presented by the administrative instructions, including a declaration of inventorship, as referred to in Rule 51*bis*.1(a)(iv), which shall be signed as prescribed by the administrative instructions.

Rule 51*bis*.1(a)(iv), provides that subject to Rule 51*bis*.2, the National Law applicable by the designated office may, in accordance with Article 37, require the Applicant to furnish,

in particular where the International application designates a state whose national law requires that national applications be filed by the Inventor, any document containing an oath or declaration of inventorship.

The International application from which the present application derives was filed with two scientists, Professor Igor Filippovich and Doctor Natalya Sorokina, named in error and without deceptive intent as inventors in the PCT Request. These scientists did not conceive the subject matter of any of the pending claims and are therefore not considered to be inventors of that subject matter. Accordingly, declarations were filed subsequently to correct this error under PCT Rule 92*bis*, which resulted in the deletion of their names from the PCT Request. *See* Exhibits A and B for copies of the declarations. Moreover, the PCT Request did not implicate *any* oath or declaration relating to inventorship that was executed by any person named in the PCT Request under PCT Rule 4.17(iv).

Since neither condition of 37 C.F.R. § 1.497(d) is satisfied here, there is no legal basis for the PTO to rely on PCT Rule 4.17(iv) to require the submission of a statement from the individuals that were deleted as inventors.

For at least these reasons, Applicants are entitled to their rightful claim of convention priority. Masci therefore is not available as prior art. Accordingly, Applicants respectfully urge the Examiner to reconsider and withdraw the rejection.

2. Willmott et al.

Claims 1 and 5-6 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Willmott et al., *Fibrinolysis*, *9*(1):1-8 (1995) ("Wilmott"). Office Action at page 7. Specifically, the Examiner alleges that Willmott teaches a preparation of a single stage competitive inhibitor of plasmin with a dissociation constant in the range of 10^{-7} M. To the extent that this rejection may apply to the claims as amended, Applicants respectfully traverse the rejection.

Willmott does not teach or suggest the claimed substantially pure preparation. Rather, this reference teaches an impure mixture of at least two plasmin inhibitors. The preparation

disclosed by Willmott was originally believed to be nearly homogeneous with respect to the plasmin inhibitor contained therein. *See* specification at page 4, lines 9-11. However, the inventors discovered that the disclosed preparation contains in fact two plasmin inhibitors, namely Txln 1 and Txln 2, that together "constitute only about 50% of the *total protein* (by weight) . . . [of the] preparation". *Id.* at lines 12-15 (emphasis added). *See also* specification at page 54, lines 17-23 (Example 1).

It logically follows that no more than 50% of the *total material* could be ascribed to a single plasmin inhibitor. The balance of the disclosed preparation "contains other compounds which may interfere with plasmin inhibition." *Id.* at page 4, lines 17-18.

By contrast, the claimed preparation is substantially pure with respect to the recited plasmin inhibitor. Specifically, the plasmin inhibitor represents at least 60% of the *total material*, not just the *total protein*. There is no question therefore that Willmott does not teach or suggest the recited level of purity for the claimed preparation. Consequently, Willmott does not anticipate the invention because the reference does not teach or suggest a substantially pure plasmin inhibitor preparation. Accordingly, Applicants respectfully urge the Examiner to reconsider and withdraw this rejection.

IV. Conclusion

The present application is now in condition for allowance. Applicants therefore respectfully request favorable reconsideration of the application as amended. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date June 22, 2004 By Steve M. Reed Reg. No. 54,393

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

for Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

FISHER ADAMS KELLY
Level 13
AMP Place
10 Eagle Street
Brisbane, QLD 4000
AUSTRALIE

Date of mailing (day/month/year)
10 November 1999 (10.11.99)

Applicant's or agent's file reference
2/2867/PC-VA

IMPORTANT NOTIFICATION

International application No.
PCT/AU99/00343

International filing date (day/month/year)
07 May 1999 (07.05.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address

FILIPPOVICH, Igor, Vladimirovich
Appartment 240
Novinsky Boulevard 18
121069 Moscou
Russian Federation

State of Nationality: RU
State of Residence: RU
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address

State of Nationality:
State of Residence:
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
THE ABOVE-MENTIONED APPLICANT INVENTOR HAS BEEN DELETED FROM THE RECORD.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
I. Britel

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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Brisbane, QLD 4000
AUSTRALIE

RECEIVED
23 NOV 1999
BY:

Date of mailing (day/month/year) 10 November 1999 (10.11.99)	
Applicant's or agent's file reference 2/2867/PC-VA	**IMPORTANT NOTIFICATION**
International application No. PCT/AU99/00343	**International filing date** (day/month/year) 07 May 1999 (07.05.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
SOROKINA, Natalya, Igorevna Appartment 240 Novinsky Boulevard 18 121069 Moscou Russian Federation	RU	RU
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
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[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer I. Britel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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